Answer 1:

Bibliographic Information

Breast cancer progression in MCF10A series of cell lines is associated with alterations in retionic acid and retinoid X receptors and with differential response to retinoids. Peng, Xinjian; Yun, Duri; Christov, Konstantin. Department of Surgical Oncology Laboratories, University of Illinois at Chicago, Chicago, IL, USA. International Journal of Oncology (2004), 25(4), 961-971. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 142:4222 AN 2004:891713 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In most breast carcinomas and in breast cancer cell lines, retinoic acid receptor β (RARβ) is lost or down-regulated, whereas retinoic acid receptor α and γ (RARα, γ) and retinoid X receptors (RXRα, β, γ) are variably expressed. Little is known about alterations of the above receptors in hyperplastic and premalignant stages of breast cancer development. In this study, we employed the MCF10A series of breast epithelial cell lines (the parental and benign MCF10A, premalignant MCF10AT, and malignant MCF10CA1a) to assess whether in the course of their malignant transformation specific alterations in RARα, β, γ and RXRα, β, γ expression occur and whether they may affect the sensitivity of cells to retinoids. Malignant properties of the above cell lines were estd. by the nude mice xenograft transplantation assay. Among the above receptors most significant alterations occurred in RARβ2, which was detected in the normal breast epithelial cells both, at mRNA and protein levels, but expressed in the MCF10A cell lines at mRNA level only. The transformation of benign MCF10A cells into premalignant MCF10AT and malignant MCF10CA1a was also assocd. with increase in RARα, RARγ, RXRα, and RXRβ proteins expression. All-trans retinoic acid (atRA), 9-cis retinoic acid (9cRA), and 4-(hydroxyphenyl) retinamide (4-HPR) induced RARβ2 protein expression exclusively in the benign MCF10A cells and the former two retinoids, mRNA expression in MCF10A and MCF10AT cells, but not in malignant, MCF10CA1a cells, suggesting that the loss of inducible RARβ expression is assocd. with the progression and malignant transformation of MCF10A cells. Retinoids also variable decreased the RARα, RARγ and RXRα protein expression preferentially in the premalignant and malignant, but not in benign MCF10A cells. Among the above retinoids, 4-HPR was most efficacious in inhibiting the growth of the three cell lines and this apparently was not dependent on the levels of the RARβ2 transcriptional activation.

Thus, our data support the hypothesis that breast epithelial cells in the course of their progression and malignant transformation may differentially respond to retinoids and that not only RARβ, but RARα, γ and/or RXRα, β may also serve as potential targets for retinoids in breast cancer prevention and therapy trials.

Answer 2:

Bibliographic Information

Regulatory effects of peroxisome proliferator-activated receptor γ on growth of pancreatic carcinoma. Dong, Yuwei; Wang, Xingpeng; Wu, Kai; Wu, Liying; Zhang, Ruling. Shanghai First People's Hospital, Shanghai Jiaotong University, Shanghai, Peop. Rep. China. Zhonghua Neike Zazhi (Beijing, China) (2003), 42(7), 479-482. Publisher: Zhonghua Yixuehui Zazhishe, CODEN: CHHNAB ISSN: 0578-1426. Journal written in Chinese. CAN 142:131689 AN 2004:454246 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of peroxisome proliferator-activated receptor (PPAR) γ activation on the growth of human pancreatic carcinoma both in vitro and in vivo were examd. The expression of PPARγ and RXRα (retinoid X receptor alpha) were examd. by RT-PCR. SW1990 pancreatic cancer cells were resp. treated with 9-cis-RA (retinoic acid), 15d-PGJ2 [15-deoxy-delta-12,14-prostaglandin-J(2)] and both of them. Antiproliferative effect was evaluated with cell viability by using MTT assay. Pancreatic cancer xenograft tumor model was established in nude mice by inoculating SW1990 cells s.c. and rosiglitazone, a PPARγ activator, was administered via water drinking in exptl. group. The nude mice were sacrificed after 75 days, the vol. and wt. of the xenograft tumor were measured. Expression of PCNA (proliferating cell nuclear antigen) was obsd. by immunohistochem. staining. RT-PCR showed that PPARγ and RXRα mRNA were expressed in SW1990 cell line. MTT assay demonstrated that 15d-PGJ2, 9-cis-RA and the combination of both had a potent

inhibitory effect on the growth of SW1990 cells in a dose-dependent manner. SW1990 cells were suppressed to more than 50% of the control at the concn. of 10 μmol/L 15d-PGJ2, 20 μmol/L 9-cis-RA, and 5 μmol/L 15d-PGJ2 plus 10 μmol/L 9-cis-RA, resp. And 9-cis-RA had a synergic action with 15d-PGJ2 on the growth inhibition of pancreatic carcinoma. In vivo studies, rosiglitazone suppressed the growth of pancreatic carcinoma in a statistically significant manner. The av. tumor vol. and tumor wt. in the exptl. group were less than those in the control group, the growth inhibition rate of rosiglitazone was 80.7%. PCNA was present in both groups, but immunohistochem. showed a down-regulation trend of PCNA in the exptl. group as compared with the control group. Activation of PPARγ exerts a neg. regulatory effect on the growth of pancreatic carcinoma both in vitro and in vivo. These results suggested that PPARγ might be a novel therapeutic target for the pancreatic carcinoma.
Activation of RXRα has a synergic action with PPARγ agonist on the growth inhibition of pancreatic carcinoma.

Answer 3:

Bibliographic Information

Combination Treatment with 1α,25-Dihydroxyvitamin D3 and 9-cis-Retinoic Acid Directly Inhibits Human Telomerase Reverse Transcriptase Transcription in Prostate Cancer Cells. Ikeda, Naoya; Uemura, Hiroji; Ishiguro, Hitoshi; Hori, Mayumi; Hosaka, Masahiko; Kyo, Satoru; Miyamoto, Ken-ichi; Takeda, Eiji; Kubota, Yoshinobu. Graduate School of Medicine, Department of Urology, Yokohama City University, Kanagawa, Japan. Molecular Cancer Therapeutics (2003), 2(8), 739-746. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 139:375535 AN 2003:665766 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The vitamin D3 receptor, which is the nuclear receptor for 1α,25-dihydroxyvitamin D3 (VD3), forms a heterodimer with the retinoid X receptor (RXR), which is the nuclear receptor for 9-cis-retinoic acid (9-cis-RA). The heterodimer binds to a specific response element consisting of two directly repeated pairs of motifs, AGGTGA, spaced by three nucleotides [direct repeat (DR) 3] and modulates the expression of VD3-responsive genes. Telomerase activity, which is seen in most immortal cells and germ cells, is a complex of enzymes that maintain the length of telomeres. One of the major components of human telomerase, human telomerase reverse transcriptase (hTERT), is the catalytic subunit, and the expression of hTERT might correlate most strongly with telomerase activity. The authors found that the sequence of 5'-AGTTCATGGAGTTCA-3' (DR3') is similar to that of DR3 in the promoter region of hTERT. The authors' results showed that the combination of VD3 and 9-cis-RA inhibited telomerase activity through direct interaction of the heterodimer of vitamin D3 receptor and RXR with the DR3' sequence in the hTERT promoter as well as the combination of VD3 and selective RXR ligand did. Also, in vivo data showed that the growth of xenografts in nude mice was inhibited by VD3 and 9-cis-RA. The results of the present study provide evidence on the mol. mechanism of the inhibition of cell growth by these agents, and they could be novel therapeutic agents for prostate cancer.

Answer 4:

Bibliographic Information

Retinoic acids reduce matrilysin (matrix metalloproteinase 7) and inhibit tumor cell invasion in human colon cancer. Adachi, Yasushi; Itoh, Fumio; Yamamoto, Hiroyuki; Iku, Shohei; Matsuno, Keiki; Arimura, Yoshiaki; Imai, Kohzoh. First Department of Internal Medicine, Sapporo Medical University, Sapporo, Japan. Tumor Biology (2001), 22(4), 247-253. Publisher: S. Karger AG, CODEN: TUMBEA ISSN: 1010-4283. Journal written in English. CAN 136:241190 AN 2001:507436 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

All-trans retinoic acid (ATRA), 9-cis retinoic acid and 13-cis retinoic acid are naturally occurring retinoids used in the prevention and therapy of various pre-neoplastic and neoplastic diseases. It was previously reported that matrilysin, one of the matrix metalloproteinases (MMP-7), plays a crit. role in the invasion and metastasis of gastrointestinal cancers. Moreover, it has been shown that ATRA down-regulates matrilysin expression and prevents in vitro invasion by colon cancer cells. In this study, three retinoids

were used, both in Matrigel invasion assays and in s.c. xenografts in mice, to evaluate the effects of retinoids on invasion by colon cancer cell lines (CHC-Y1, DLD-1, HT-29, BM314, CaR-1 and WiDr). All three retinoic acids tested reduced matrilysin expression and suppressed the invasiveness of colon cancer cell lines in vitro. Retinoic acids also reduced tumor invasion in mice without influencing tumor growth. Matrilysin expression in these tumors was clearly reduced. These data support the use of retinoic acids as useful reagents to manage patients with colorectal carcinoma.

Answer 5:

Bibliographic Information

Effect of all-trans- and 9-cis-retinoic acid on growth and metastasis of xenotransplanted canine osteosarcoma cells in athymic mice. Hong, Sung-Hyeok; Kadosawa, Tsuyoshi; Mochizuki, Manabu; Matsunaga, Satoru; Nishimura, Ryohei; Sasaki, Nobuo. Pediatrics Oncology Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, MD, USA. American Journal of Veterinary Research (2000), 61(10), 1241-1244. Publisher: American Veterinary Medical Association, CODEN: AJVRAH ISSN: 0002-9645. Journal written in English. CAN 134:275415 AN 2000:766497 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of all-trans- and 9-cis-retinoic acid (RA) were studied on tumor growth and metastatic ability of canine osteosarcoma cells transplanted into athymic (nude) mice. All-trans RA (3 or 30 μg/kg), 9-cis RA (3 or 30 mg/kg), or sesame oil (0.1 mL; control treatment) was administered intragastrically 5 days/wk for 4 wk beginning 3 days after transplantation or after formation of a palpable tumor. Two weeks after the final treatment, the mice were euthanized, and the no. of mice with pulmonary metastases was detd. No adverse treatment effects were detected. Tumor wt. was less in mice treated with either dose of 9-cis RA than in control mice, although this difference was not significant. Treatment with 30 mg 9-cis RA/kg, initiated after tumor formation, reduced the incidence of pulmonary metastases, compared with the control group. Thus, 9-cis RA decreased the incidence of pulmonary metastases in nude mice transplanted with canine osteosarcoma cells and may be a potential adjunct therapy for treatment of osteosarcoma in dogs.

Answer 6:

Bibliographic Information

A novel retinoic acid receptor-selective retinoid, ALRT1550, has potent antitumor activity against human oral squamous carcinoma xenografts in nude mice. Shalinsky, David R.; Bischoff, Eric D.; Lamph, William W.; Zhang, Lin; Boehm, Marcus F.; Davies, Peter J. A.; Nadzan, Alex M.; Heyman, Richard A. Departments Retinoid Research, Ligand Pharmaceuticals, Inc., San Diego, CA, USA. Cancer Research (1997), 57(1), 162-168. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 126:139556 AN 1997:40439 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have identified a novel retinoid, ALRT1550, that potently and selectively activates retinoic acid receptors (RARs). ALRT1550 binds RARs with Kd values of .simeq.1-4 nM, and retinoid X receptors with low affinities (Kd .simeq. 270-556 nM). We studied the effects of ALRT1550 on cellular proliferation in squamous carcinoma cells. ALRT1550 inhibited in vitro proliferation of UMSCC-22B cells in a concn.-dependent manner with an IC50 value of 0.22 ± 0.1 (SE) nM. 9-Cis-Retinoic acid (ALRT1057), a pan agonist retinoid that activates RARs and retinoid X receptors, inhibited proliferation with an IC50 value of 81 ± 29 nM. In vivo, as tumor xenografts in nude mice, UMSCC-22B formed well-differentiated squamous carcinomas, and oral administration (daily, 5 days/wk) of ALRT1550, begun 3 days after implanting tumor cells, inhibited tumor growth by up to 89% in a dose-dependent manner over the range of 3-75 μg/kg. ALRT1550 (30 μg/kg) also inhibited growth of established tumors by 72 ± 3% when tumors were allowed to grow to .simeq.100 mm3 before dosing began. In comparison, 9-cis-retinoic acid at 30 mg/kg inhibited growth of established tumors by 73 ± 5%. Interestingly, retinoids did not appear to alter tumor morphologies in UMSCC-22B tumors. Notably, ALRT1550 produced a therapeutic index of .simeq.17 in this model, indicating a sepn. between doses that inhibited tumor growth and that induced symptoms of

hypervitaminosis A. In summary, ALRT1550 potently inhibits cellular proliferation in vitro and in vivo in this squamous cell carcinoma tumor model. These data support addnl. study of ALRT1550 for its potential for improving anticancer therapy in human clin. trials.

Answer 7:

Bibliographic Information

Enhanced antitumor efficacy of cisplatin in combination with ALRT1057 (9-cis retinoic acid) in human oral squamous carcinoma xenografts in nude mice. Shalinsky, David R.; Bischoff, Eric D.; Gregory, Margaret L.; Lamph, William W.; Heyman, Richard A.; Hayes, J. Scott; Thomazy, Vilmos; Davies, Peter J. A. Departments Retinoid and Endocrine Research, Ligand Pharmaceuticals, Inc., San Diego, CA, USA. Clinical Cancer Research (1996), 2(3), 511-20. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 124:331989 AN 1996:208597 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Cisplatin (DDP) is commonly used to treat head and neck tumors. Therapy frequently fails due to development of DDP resistance or toxicities assocd. with DDP therapy. In this study, effects of ALRT1057 [9-cis retinoic acid (9-cis RA)] on DDP cytotoxicity were studied in a human oral squamous carcinoma xenograft model. Mice bearing xenografts were dosed p.o. daily 5 days/wk with 30 mg/kg 9-cis RA and/or i.p. twice weekly with 0.3-0.9 mg/kg DDP. Max. tolerated doses of 9-cis RA and DDP were approx. 60 and ≥2.9 mg/kg, resp., under their dosing schedules and routes of administration. Control tumors grew rapidly with mean doubling times of 4 days and reached mean vols. of 1982 mm3 after 24 days. DDP at doses of 0.3, 0.45, and 0.9 mg/kg inhibited tumor growth by 28, 47, and 86%, resp., 24 days after tumor cell implantation. Thirty mg/kg 9-cis RA inhibited tumor growth by 25%. In combination, 0.3 mg/kg DDP + 30 mg/kg 9-cis RA inhibited tumor growth by 68%; 0.45 mg/kg DDP + 30 mg/kg 9-cis RA inhibited growth by 78%. These decreases were greater than those that would have been produced by either agent summed sep. Of importance, at doses of 9-cis RA that enhanced DDP cytotoxicity, no change in dose tolerance was obsd. as compared to tolerances obsd. for either agent alone, indicating that 9-cis RA increased sensitivity to DDP without altering systemic toxicity. In addn., 9-cis RA profoundly altered squamous cell carcinoma phenotypes by suppressing squamous cell differentiation, resulting in tumors with increased nos. of basal cells. In contrast, DDP selectively depleted proliferating basal cells from carcinomas. In combination, morphol. changes produced by 9-cis RA alone predominated, suggesting a possible basis for enhanced DDP sensitivity in tumors exposed to both agents. These data demonstrate that 9-cis RA enhances tumor sensitivity to DDP, and suggest that this combination should be tested in Phase I-II clin. trials for its potential for improving anticancer therapy of squamous cell cancers.

Answer 8:

Bibliographic Information

Retinoid-induced suppression of squamous cell differentiation in human oral squamous cell carcinoma xenografts (line 1843) in athymic nude mice. Shalinsky, D. R.; Bischoff, E. D.; Gregory, M. L.; Gottardis, M. M.; Hayes, J. S.; Lamph, W. W.; Heyman, R. A.; Shirley, M. A.; Cooke, T. A.; et al. Dep. of Retinoid Res., Ligand Pharmaceuticals, Inc., San Diego, CA, USA. Cancer Research (1995), 55(14), 3183-91. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 123:102236 AN 1995:688170 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Retinoids are promising agents for therapy of squamous cancers. In vitro, retinoids decrease expression of differentiation markers in head and neck squamous carcinoma cells. Little information is available on effects of retinoids on head and neck squamous carcinoma cell xenograft growth in vivo. To address this issue, head and neck squamous carcinoma cells (line 1843) were established as xenografts in nude mice. Control tumors grew rapidly with doubling times of 4-6 days to mean vols. of 1696 mm3 after 24 days. Histol. analyses indicated the formation of well-differentiated squamous carcinoma cells exhibiting pronounced stratification (basal and suprabasal cells) and keratinization (keratin pearls) with abundant stroma. Cytokeratin 19 expression was restricted to the basal cell layers, and cytokeratin 4 expression was abundant in suprabasal cells. Mice were treated daily with 30 mg/kg 9-cis retinoic acid, 20

mg/kg all-trans-retinoic acid, or 60 mg/kg 13-cis retinoic acid by p.o. gavage on a schedule of 5 days/wk over 4 wk. Low micromolar (1.48-3.67 μM) and nanomolar (200-400 nM) concn. of 9-cis retinoic acid and all-trans-retinoic acid were measured in plasmas and xenografts, resp., 30 min after dosing. Retinoid treatment produced a marked suppression of the squamous cell differentiation of tumor cells manifested by decreased keratinization, loss of stratification, and accumulation of basal cells. This was accompanied by large decreases in the no. of CK-4 pos. cells and concomitant increases of CK19-pos. cells. Retinoic acid receptor-β expression was also increased by 2.9-9.7-fold after chronic retinoic treatment. 9-Cis retinoic acid and all-trans-retinoic acid decreased tumor vols. by 23 ± 5 (SE0 and 19 ± 3%, resp. P ≤ 0.050); 13-cis retinoic acid was inactive. These retinoids did not decrease the rate of exponential tumor growth but increased the latent period until exponential growth began.
These studies demonstrate that the retinoids do not universally decrease tumor growth but profoundly suppress squamous cell differentiation in vivo in this xenograft model.

Answer 9:

Bibliographic Information

Activity of MDI-301, a novel synthetic retinoid, in xenografts. Appleyard Virginia C L; O'Neill Mary A; Murray Karen E; Bray Susan E; Thomson George; Kernohan Neil M; Varani James; Zhang Jian; Thompson Alastair M Department of Surgery, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK Anti-cancer drugs (2004), 15(10), 991-6. Journal code: 9100823. ISSN:0959-4973. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 15514569 AN 2004605065 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The efficacy of MDI-301, a non-toxic novel synthetic retinoid, was found to be equivalent to the natural 9-cis-retinoic acid (RA) in vitro against estrogen-dependent MCF7 and T47D breast cancer cell lines which express RA receptor (RAR) alpha. Both retinoids also showed similar efficacy against established PC-3 prostate carcinoma xenografts. MCF7 tumor xenografts showed a reduction in tumor growth of 48% without systemic side-effects upon treatment with MDI-301 compared with MCF7 controls. Tumor xenografts derived from MDA-MB-231, an estrogen-independent breast cancer cell line that expresses low levels of RARalpha, were unresponsive. This study demonstrates that MDI-301 is as efficacious as 9-cis-RA against cancer cells with RARalpha, with no signs of toxicity in vivo, making it a potential candidate for cancer therapy.

Answer 10:

Bibliographic Information

The vitamin A analogues: 13-cis retinoic acid, 9-cis retinoic acid, and Ro 13-6307 inhibit neuroblastoma tumour growth in vivo. Ponthan F; Borgstrom P; Hassan M; Wassberg E; Redfern C P; Kogner P Department of Woman and Child Health, Karolinska Hospital, Stockholm, Sweden. frida.ponthan@lab.ks.se Medical and pediatric oncology (2001), 36(1), 127-31. Journal code: 7506654. ISSN:0098-1532. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 11464864 AN 2001414886 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Neuroblastoma, a childhood tumour of the sympathetic nervous system, may undergo spontaneous differentiation or regression due to apoptosis after no or minimal therapy. However, the majority of neuroblastomas are diagnosed as metastatic tumours with a poor prognosis in spite of intensive multimodal therapy. Vitamin A and its analogues (retinoic acid, RA) play an important role in normal cel lular differentiation and programmed cell death. RA regulates neuroblastoma growth and differentiation in vitro, and has shown activity against human neuroblastoma in vivo.

PROCEDURE: Recently, 9-cis RA was shown to induce apoptosis in vitro in neuroblastoma using a 5 days short-term treatment and subsequent washout. In the present study, nude rats with human neuroblastoma SH-SY5Y xenografts were treated with 13-cis RA (4 mg po daily), 9-cis RA (5 mg po daily) or the novel analogue Ro 13-6307 (0.3 mg po daily) using either a continuous or short-term schedule. RESULTS: ALL three different retinoids decreased neuroblastoma growth significantly in terms of tumour weight after 8-12 days when compared to untreated controls ($P < 0.05$). Minor signs of toxicity in 13-cis RA treated rats were observed. However, severe toxicity with significant weight loss was seen in all rats treated with 9-cis RA and Ro 13-6307. Toxicity was more pronounced with the continuous regimen. CONCLUSIONS: We conclude that different retinoids reduce neuroblastoma tumour growth in vivo. Drug scheduling and dosage may affect both therapeutic efficacy and toxic side effects. Further in vivo studies are warranted, including pharmacokinetic and molecular analyses, before clinical trials with promising retinoids like 9-cis RA and Ro 13-6307 can be started in children with neuroblastoma.